Taoka et al. is relied upon to report a process for producing simvastatin which comprises treating lovastain with an inorganic base and a secondary or tertiary alcohol to give a triol acid; serially acidifying and lactonizing the triol acid to give a diol lactone; subjecting the resulting diol lactone to selective protection with a ketal or acetal protective group; and acylating and deprotecting to give simvastatin.

Dabora et al. is relied upon to teach a process for the preparation of simvastatin, which comprises sequential acylation of a diol lactone to form a bis acylated intermediate, followed by selective deacylation, and lactone ring closure to form simvastatin.

The invention recited in pending claims 1 to 8, is directed to a method of preparing simvastatin comprising the steps of: (a) treating lovastatin of formula (II) with potassium hydroxide dissolved in a mixture of water and methanol to obtain a triol acid of formula (III); (b) relactonizing the triol acid of formula (III), and protecting the hydroxy group on the lactone ring; and (c) acylating the resulting compound of formula (V) with 2,2-dimethylbutyryl chloride or 2,2-dimethylbutyryl bromide in the presence of an acylation catalyst in an organic solvent, followed by removing the silyl protecting group on the lactone ring to obtain simvastatin of formula (I). The method allows a production of highly pure simvastatin in a high yield at a low production cost.

The presently claimed invention would not have been obvious over Hoffman et al. taken with Taoka et al. in view of Dabora et al., because the inventive method is different from the processes of the cited references, in terms of, among others, the hydrolysis step (a) and the acylation step (c).

The inventive method recited in claim 1 produces highly pure simvastatin in a high yield, by using potassium hydroxide dissolved in a mixture of water and methanol in the hydrolysis step (a) and an acylation catalyst in the acylation step (c). That is, in the inventive method, the hydrolysis step (a) is performed using a mixture of potassium hydroxide, methanol and water (ternary system), giving a triol acid (compound of formula (III)) having a purity of at least 98%, in a high yield of at least 95%, and the acylation step is carried out in the presence of an acylation catalyst which facilitates the completion of the reaction, shortening the process time.

In contrast, the method of Hoffman et al. involves a hydrolysis step using aqueous $LiOH \cdot H_2O$; and an acylation step using 2,2-dialkylbutyryl acid, which is carried out in the absence of an acylation catalyst.

i) Hydrolysis step

In this regard, the Office Action has pointed out that Hoffman et al. use lithium hydroxide instead of potassium hydroxide in the hydrolysis step, but the use of lithium hydroxide or potassium hydroxide in an analogous process is taught by Taoka et al.

However, the Examiner's attention is invited to the fact that in the present invention, the hydrolysis step is performed using a ternary mixture of potassium hydroxide, methanol and water. In contrast, Hoffman does not teach or suggest the use of the ternary system.

Furthermore, although the use of lithium hydroxide or potassium hydroxide is disclosed in Taoka et al., the method of Taoka et al. differs from that of the present invention in that Taoka's method uses a binary system, which is a mixture of lithium hydroxide or potassium hydroxide and a secondary or tertiary alcohol (*see* column 6 lines 42 and 43 of Taoka et al.).

Taoka also does not teach a use of primary alcohol in the ternary system as recited in claim 1 of the present application.

Accordingly, the hydrolysis condition of the present invention would not have been obvious even when Hoffman et al. with Taoka et al. are combined.

ii) Acylation step

As for the acylation step, the Examiner has pointed out that the method of Hoffman et al. uses a tetrabutylammonium fluoride instead of tetrabutylammonium bromide used in the present invention as an acylation catalyst, and Dabora et al. teaches an analogous process for acylating using 2,2-dimethylbutyryl acid or the 2,2-dimethylbutyryl chloride derived therefrom.

However, tetrabutylammonium fluoride used in Hoffman et al. is used not as an acylation catalyst but as an agent to facilitate the deprotection of tert-butyldimethylsilyl (TBDMS) (*see* column 14 lines 3 and 4 of Hoffman et al.), and, therefore, Hoffman et al. fail to render the present invention obvious even if combined with Dabora et al.

Accordingly, the present invention is not taught or suggested by Hoffman et al., Taoka et al., and Dabora et al., either alone or in combination.

iii) Effects

The hydrolysis step according to the inventive method gives the triol acid (compound of formula (III)) with a high purity, for example at least 98%, in a high yield, for example, at least 95%. *See* page 6 lines 24 to 27 in the specification. As the result, simvastatin is obtained in a high purity (e.g., at least 99%) and in a high yield (e.g., 90% or higher). *See* Example 1 of the present invention.

In contrast, it is reported that the method of Hoffman et al. requires a high temperature and a long reaction time of 56 hours for the hydrolysis procedure, which leads to a number of undesired by- products, causing low yield (about 83%) and low purity of the final product (*see* column 13 line 60, and Examples 2 and 5 of Hoffman et al.), which is markedly lower than that of the present invention.

Further, triol acid obtained by the hydrolysis step according to the Taoka et al. method is reported to be obtained as a brown-colored oil (*see* column 4 lines 16 to 18 and column 6 lines 49 and 50 of the Taoka et al. publication). In this regard, a skilled person in the art can reasonably presume that the oil product obtained by Taoka et al. is of an impure form.

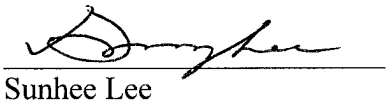
Accordingly, it is believed that the technical constitution of the presently claimed invention and effect derived therefrom would not have been obvious over Hoffman et al. taken with Taoka et al. in view of Dabora et al., and, therefore, it is believed that the 103 rejection is not sustainable.

In view of the foregoing discussions, it is respectfully submitted that the present invention as recited in the presently pending claims 1 to 8 would not have been obvious over the teachings contained in the references relied upon by the Office Action, either alone or in combination, and, therefore, it is earnestly requested that the Office Action's rejection be withdrawn and the pending claims be allowed in their present form.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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